



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

⑪ Publication number:

0 139 202  
A1

⑫

## EUROPEAN PATENT APPLICATION

⑬ Application number: 84110712.1

⑮ Int. Cl. 4: G 01 N 15/08

⑭ Date of filing: 07.09.84

G 01 M 3/26, B 01 D 13/00  
A 61 L 2/02, G 01 F 23/28

⑯ Priority: 09.09.83 JP 167343/83  
19.03.84 JP 53259/84

⑰ Inventor: Akashi, Takamichi  
No. 2-2-10, Midorigaoka  
Ikeda-shi Osaka 563(JP)

⑲ Date of publication of application:  
02.05.85 Bulletin 85/18

⑰ Inventor: Ikuta, Akio  
No. 1-3-17-502, Tomobuchi-cho Miyakojima-ku  
Osaka-shi Osaka 534(JP)

⑳ Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

⑰ Inventor: Sasaki, Isao  
No. 2-8-19, Sakuragaoka  
Minoo-shi Osaka 562(JP)

㉑ Applicant: Fujisawa Pharmaceutical Co., Ltd.  
3, Doshomachi 4-chome Higashi-ku  
Osaka-shi, Osaka 541(JP)

⑰ Inventor: Fukuda, Hiroshi  
No. 4-1-2, Narimasu  
Itabashi-ku Tokyo 175(JP)

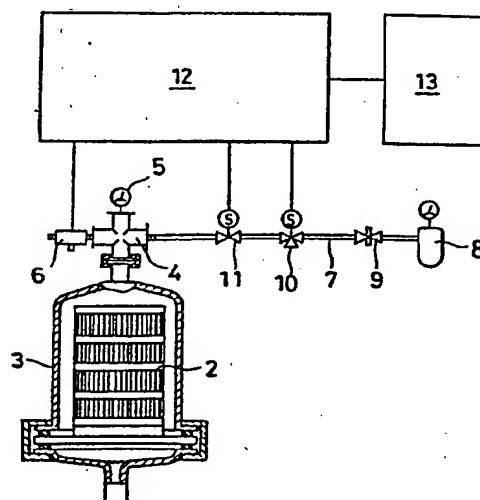
㉒ Inventor: Hirayama, Shigemitsu  
No. 2-145-9, Minami Yuge-cho  
Yao-shi Osaka 581(JP)

㉓ Representative: Patentanwälte TER MEER - MÜLLER -  
STEINMEISTER  
Mauerkircherstrasse 45  
D-8000 München 80(DE)

㉔ Method of and apparatus for testing membrane filters, and apparatus for sterilizing liquids with use of membrane filter.

㉕ A membrane filter testing method comprises increasing the pressure at the primary side of a membrane filter fixedly accommodated in a housing and wetted with a liquid, by a gas at a predetermined rate, and checking whether the pressure at the primary side of the membrane filter is within a specified judging range after lapse of a predetermined period of time.

FIG.1



METHOD OF AND APPARATUS FOR TESTING MEMBRANE FILTERS,  
AND APPARATUS FOR STERILIZING LIQUIDS WITH USE OF  
MEMBRANE FILTER

The present invention relates to a method of and  
5 an apparatus for testing membrane filters, and an apparatus  
for sterilizing liquids with use of a membrane filter.

A filtration process for sterilizing liquids with  
use of membrane filters is needed for preparing injection  
solutions and other liquid pharmaceuticals or for sterilizing  
10 industrial water. This process requires testing of the  
membrane filter for perfection and removal of air from the  
filter housing. To carry out the liquid sterilizing filtration  
process automatically, the automation of the filter  
perfection test and the deaeration of the filter housing is  
15 essential, but extreme difficulties are encountered in  
automating these steps as will be described later.

A description will be given of the conventional

sterilizing filtration process for pharmaceutical liquids, especially membrane perfection test and filter housing deaeration.

First in a substerilization chamber, a medicinal liquid is sent from a preparation container through a filter for rough filtration into a primary receptacle (container) which has been cleaned and sterilized. On the other hand, a secondary receptacle (container) cleaned for containing the sterilized filtrate and a filter housing are placed into a sterilization chamber through a sterilizer provided between the substerilization chamber and the sterilization chamber. The filter housing has enclosed therein a cartridge membrane filter and is provided with tubes connected to the primary side and the secondary side of the filter.

The membrane filter is tested for perfection in the sterilization chamber. The bubble point test (hereinafter referred to as "BPT") standardized according to ASTM-F316-70 is widely used as a method of testing membrane filters without entailing breaking or contamination and with ease and good reproducibility. According to BPT, the pores of the filter are regarded as capillary tubes, and the maximum radius of the pores is determined by measuring pressure, based on the relationship between the pressure and the maximum pore radius expressed by the equation (I) of surface tension given below. Conventionally this test

is carried out in the following manner. First, the primary-side tube of the filter housing is connected to a gas source, such as an air, nitrogen or carbon dioxide source, via an indicating pressure gauge and a ball valve, while the forward end of the secondary-side tube of the housing is placed into water in a container. Prior to testing, the filter is impregnated with a liquid, such as distilled water, to fill the filter pores with the liquid by capillarity.

With the valve opened to a suitable extent, the primary side of the filter is gradually pressurized with the gas. While checking the housing for leakage with the unaided eye, the operator observes the pressure gause and the end of the secondary-side tube. While the gas pressure applied to the primary side of the filter is relatively low, the pressure remains in an equilibrium with the liquid in the filter pores, so that the displacement of the liquid from the pores is negligible. When the pressure reaches a level, the liquid in large pores is forced out from the pores toward the primary side. This can be recognized from bubbles released from the end of the secondary-side tube. The pressure at this time is taken as bubble point pressure (hereinafter referred to as "BP pressure"). The relationship between this pressure  $P$  and the maximum radius  $r$  of filter pores is expressed by the following surface tension equation (I):

$$r = k (2\sigma \cos \theta / P) \quad (I)$$

where  $\sigma$  is surface tension,  $\theta$  is contact angle, and  $k$  is a shape correction factor. Accordingly the filter pore size can be calculated from the BP pressure measurement as above. With the above method, however, it is necessary for the 5 operator to observe the pressure gauge and the tube end at all times until the secondary-side tube releases bubbles and to read the pressure upon the release of bubbles. The procedure is therefore very cumbersome and involves extreme difficulties in automation. Further apparatus proposed for 10 automatically testing membrane filters for perfection include one which is adapted to measure the rate of flow of diffused gas toward the secondary side of the filter when a pressure of about 80% of the BP pressure is applied to its primary side, or one which is adapted to detect the BP pressure 15 reached by intermittently applying pressure to the primary side of the filter and measuring the variations in the pressure. The former apparatus nevertheless has the problem that the measurement varies with the filtering area of the filter and involves a greater error in the case of smaller 20 filters. The latter apparatus has the problem that the measuring condition differs with the capacity of the housing. In either case, the delicate test condition setting needed renders the apparatus complex, expensive and difficult to maintain. Further although the test itself is conducted 25 automatically, the acceptability of the filter as to its

perfection must be determined by the operator based on the measurement. Accordingly it is extremely difficult to incorporate such a conventional apparatus into a line as an in-line filter testing apparatus.

5        When the perfection test for the membrane filter is completed, the primary-side tube of the filter housing is passed through the wall between the substerilization chamber and the sterilization chamber and is connected to the primary receptacle in the former chamber, and the  
10      secondary tube is connected to the secondary receptacle in the sterilization chamber to remove air from the housing, i.e. to discharge air from the primary side of the filter to ensure the filtering area of the filter. This is done by sending the medicinal liquid from the primary receptacle  
15      to the primary side of the housing, with the upper end of the housing held open. When the medicinal liquid is sent to the primary side of the housing, the air therein is discharged from the upper end of the housing, allowing the liquid level to gradually rise within the housing. While  
20      observing the liquid level, the operator closes the housing upper end upon the liquid level passing over the filter to complete deaeration. Thus, it is necessary for the operator to observe the liquid level within the housing at all times also during deaeration, so that the procedure is cumbersome  
25      and very difficult to automate.

After the filter housing is completely deaerated, the medicinal liquid is passed from the primary receptacle to the secondary receptacle continuously through the filter within the housing thus deaerated, whereby the liquid is  
5 sterilized by filtration.

When the medicinal liquid in one primary receptacle is completely filtered in this way, the primary and secondary receptacles are disconnected from the tubes of the filter housing. The secondary receptacle containing the sterilized  
10 liquid is carried to a filling machine within the sterilization chamber for filling. Before other primary and secondary receptacles are used for sterilizing medicinal liquid, membrane filter perfection test and filter housing deaeration must be carried out manually as above. The medicinal liquid  
15 may be sterilized and filled at the same time with use of a buffer tank connected to the filling machine, in place of the secondary receptacle. Even in this case, the membrane filter perfection test and filter housing deaeration must be conducted manually as above every time the liquid in one  
20 primary receptacle has been sterilized.

An object of the present invention is to provide a method of testing membrane filters for perfection easily and accurately and an apparatus for practicing this method.

Another object of the invention is to provide

a filtration apparatus for sterilizing liquids automatically with savings in labor.

The membrane filter testing method of this invention is characterized by increasing the pressure of primary side of a membrane filter, fixedly enclosed in a housing and wetted with a liquid, by a gas at a predetermined rate, and checking after lapse of a predetermined period of time whether the pressure of the primary side of the membrane filter is within a specified judging range.

10       The membrane filter testing apparatus of the present invention is characterized in that the apparatus comprises a gas source connectable to the primary side of a membrane filter fixedly enclosed in a housing and wetted with a liquid, pressure increase rate setting means positionable between the gas source and the primary side of the membrane filter to maintain the rate of increase of the pressure at the primary side of the membrane filter by the gas at a specified value, and a pressure sensor positionable at the primary side of the membrane filter.

15       We have carried out research on the membrane filter perfection test and accomplished the present invention based on the following finding. When the pressure of the primary side of a flawless filter wetted with a liquid is increased at a predetermined rate by a gas, the amount of supply of  
20       the gas from the primary side remains in an equilibrium with

the amount of discharge of the gas to the secondary side after the primary side has reached the BP pressure, so that the pressure of the primary side is maintained at a constant level. In this case, the time taken for the pressure of  
5 the primary side of the flawless filter to reach the BP pressure is substantially definite and is dependent on the BP pressure of the filter and the rate of increase of the pressure. Accordingly the filter can be tested for perfection easily and accurately by checking whether the primary-  
10 side pressure is within a specified judging range after the lapse of a predetermined period of time which is longer than the above-mentioned time. Experiments have shown that the perfection of filters can be determined quantitatively with no error between the measurement thus obtained and the  
15 measurement obtained by the conventional BPT method. The pressure may be checked by the operator with reference to a pressure gauge after the lapse of the predetermined period of time, or to a recorder which records the primary-side pressure until the predetermined period elapses. Alternatively,  
20 the pressure may be checked by automatic means after the lapse of the time period.

The test method of the invention can be conducted merely by increasing the pressure of the primary side of a membrane filter, fixedly enclosed in a housing and wetted  
25 with a liquid, by a gas at a predetermined rate and checking

whether the primary-side pressure is within a specified judging range after the lapse of a predetermined period of time. Accordingly the primary-side pressure need not always be monitored during the rise of pressure, and yet the filter 5 can be tested for perfection with ease and accuracy. Thus, even when the pressure is checked by the operator, the pressure gauge and the bubble detecting tube end need not be observed at all times unlike the conventional practice. This greatly lessens the burden on the operator. Further 10 when the pressure is checked by automatic means, the pressure after the lapse of the predetermined time period need to be compared only with the upper and lower limits of the judging range. This greatly simplifies the construction of the apparatus, especially that of electronic circuit for 15 automatic control and checking. The present invention further facilitates in-line testing because a gas source and a pressure sensor only are connected to the primary side of the housing and there is no need to connect the bubble detecting tube conventionally used to the secondary side. 20 The present test apparatus has a simple construction including a gas source, pressure increase rate setting means and pressure sensor and is also greatly simplified in its electronic circuit as mentioned above. The apparatus is therefore inexpensive to make, easy to maintain and also 25 easy to incorporate into a line an as in-line automatic

0139202

tester.

When the primary-side pressure of the membrane filter is increased, it is desirable to interrupt the increase of the pressure for a predetermined period of time 5 upon the primary-side pressure reaching a predetermined level lower than the lower limit of the judging range and to check whether the primary-side pressure decreases during the interruption. It is then possible to check the housing and the piping system for improper sealing and the filter for 10 inadequate wetting.

The present invention provides a liquid sterilizing filtration apparatus comprising a filter housing for fixedly accommodating a membrane filter therein, a primary container for containing a prefilter, a primary pipe connecting the 15 primary side of the filter housing to the primary container, a secondary container for containing a filtrate, and a secondary pipe connecting the secondary side of the filter housing to the secondary container, the apparatus being characterized in that a steam source, a gas source and a 20 distilled water source are connected to the primary pipe via a change-over valve, pressure increase rate setting means being provided between the gas source and the change-over valve for maintaining the rate of increase of the pressure at the primary side of the membrane filter by a gas 25 at a predetermined value, an air outlet being provided at an

0139202

upper portion of the filter housing and openable by a valve, a pressure sensor being provided at the primary side of the filter housing.

The filtration apparatus of the present invention  
5 is adapted to automatically test a membrane filter for per-  
fection in a process for sterilizing a liquid by filtration,  
so that the liquid can be sterilized automatically at a  
reduced cost, with savings in labor and with improved  
reliability.

10 The invention further provides a liquid sterilizing  
filtration apparatus comprising a filter housing for fixedly  
accommodating a membrane filter therein, a primary container  
for containing a prefilt, a primary pipe connecting the  
primary side of the filter housing to the primary container,  
15 a secondary container for containing a filtrate, and a  
secondary pipe connecting the secondary side of the filter  
housing to the secondary container, the apparatus being  
characterized in that a steam source, a gas source and a  
distilled water source are connected to the primary pipe  
20 via a change-over valve, pressure increase rate setting  
means being provided between the gas source and the change-  
over valve for maintaining the rate of increase of the  
pressure at the primary side of the membrane filter by a gas  
at a predetermined value, an air outlet being provided at an  
25 upper portion of the filter housing and openable by a valve,

a liquid level sensor being provided on the filter housing and positioned above the membrane filter, a pressure sensor being provided at the primary side of the filter housing.

The filtration apparatus of the invention is  
5 adapted for automatic membrane perfection testing and also for automatic removal of air from the filter housing, whereby liquid sterilizing filtration can be automatically carried out with improved efficiency.

Other features of the present invention will become  
10 apparent from the following description.

Fig. 1 is a diagram showing the piping system of a membrane filter testing apparatus embodying the invention;

Figs. 2, 3 and 4 are graphs respectively showing three examples of results obtained by testing membrane  
15 filters;

Fig. 5 is a diagram showing the piping system of a medicinal liquid sterilizing filtration apparatus embodying the invention;

Fig. 6 is an enlarged side elevation showing the  
20 main portion of a liquid level sensor in Fig. 5; and

Figs. 7, 8 and 9 are views in vertical section showing different modifications of the membrane filter and the filter housing shown in Fig. 5.

0139202

Fig. 1 shows an off-line testing apparatus which is not incorporated into a line. The apparatus is connected in the following manner to the primary side of a housing 3 accommodating a cartridge membrane filter 2 therein. One end of a cross joint 4 is joined to the primary side of the housing 3. An indicating pressure gauge 5 and a pressure sensor 6 which comprises a strain gauge or the like are connected to other two ends of the joint 4. A gas source 8 is connected to the remaining end of the joint 10 by a pipe 7. Mounted on the pipe 7 are a pressure increase rate setting valve 9 comprising a needle valve, a three-way electromagnetic valve (three-way valve) 10 and a two-way electromagnetic valve (two-way valve) 11 which are arranged from the gas source 8 toward the joint 4 in the order mentioned. The three-way valve 10 has one port which is held open to the atmosphere. The pressure sensor 6, the three-way valve 10 and the two-way valve 11 are connected to a control circuit 12, which has connected thereto an automatic recorder 13.

20 The operation of the testing apparatus will be described below with reference to a case wherein a membrane filter having a pore size of 0.2 micron is tested for perfection. Flawless hydrophilic membrane filters of cellulose ester, nylon 6/6 or polyvinylidene fluoride, which 25 are 0.2 micron in pore size, are about  $3.5 \text{ kg/cm}^2$  in BP

0139202

pressure.

Before testing, the two-way valve 11 is closed, and the three-way valve 10 is so set as to pass a gas therethrough from the setting valve 9 toward the two-way 5 valve 11. Further prior to testing, the operator opens the setting valve 9 to a degree to give a predetermined rate of increase of pressure, i.e.  $1 \text{ kg/cm}^2$  per second. A filter 2 wetted with a liquid is placed in the housing 3.

When the start switch is depressed in this state, 10 the filter is tested automatically in the following manner, and the pressure at the primary side of the housing 3 automatically detected by the sensor 6 during testing is recorded on the recorder 13 as seen in Figs. 2 to 4, in which the time (second) is plotted as abscissa vs. the primary- 15 side pressure ( $\text{kg/cm}^2$ ) of the housing 3 as ordinate.

Upon depression of the start switch, the two-way valve 11 is opened first, permitting supply of gas from the gas source 8 to the primary side of the housing 3. When the filter 2 is free from flaws and properly installed, the 20 primary-side pressure increases at the above-mentioned rate as represented by straight line a in Figs. 2 and 3. When the pressure increases to  $2 \text{ kg/cm}^2$ , the two-way valve 11 is closed to interrupt the increase of pressure for a predetermined period of time ( $t_2 = 20$  seconds). If the 25 housing 3 or the piping is improperly sealed or the filter

0139202

2 is improperly wetted, the primary-side pressure decreases from  $2 \text{ kg/cm}^2$  during the interruption, so that an alarm is given to interrupt the test. In the absence of such an abnormality, the primary-side pressure remains at a constant level as indicated by straight line b in Figs. 2 and 3, and upon lapse of the time  $t_2$ , the two-way valve 11 is opened to resume increase of pressure. A predetermined period of time ( $t_3 = 60$  seconds) after the resumption of pressure increase, the primary-side pressure is automatically checked as to whether it is in a specified judging range ( $3.5 \pm 0.5 \text{ kg/cm}^2$ ).

When the filter is flawless and 0.2 micron in pore size, the primary-side pressure increases at the foregoing rate after the resumption of pressure increase as indicated by straight line c in Fig. 2, and is maintained at a constant level as indicated by straight line d in Fig. 2 after reaching the BP pressure ( $3.5 \text{ kg/cm}^2$ ). Since the pressure ( $3.5 \text{ kg/cm}^2$ ) obtained upon lapse of the time  $t_3$  after the restart of pressure increase is within the judging range of  $3.5 \pm 0.5 \text{ kg/cm}^2$ , the filter is found to be normal, a normality lamp is turned on, and the three-way valve 10 is operated to discharge air from the primary side of the housing 3 into the atmosphere via the valve 10, whereby the test is completed.

If the filter is larger than 0.2 micron in pore

size, for example, when a filter having a pore size of 0.45 micron is installed by mistake, the primary-side pressure increases at the above rate after the restart of pressure increase as indicated by straight line e in Fig. 3 and 5 remains constant after reaching a BP pressure of  $2.4 \text{ kg/cm}^2$  as indicated by straight line f in Fig. 3. The pressure ( $2.4 \text{ kg/cm}^2$ ) obtained upon the lapse of the above-mentioned time  $t_3$  after the restart of pressure increase is lower than the lower limit ( $3 \text{ kg/cm}^2$ ) of the judging range, so that a 10 judgment of abnormality is given, the alarm goes on, and then the pressure is further maintained for a predetermined period of time ( $t_4 = 40$  seconds) to clearly identify the abnormality. In the same manner as above, the gas is discharged from the primary side to complete the test.

15 Conversely, when the filter is smaller than 0.2 micron in pore size, for example, when a filter having a pore size of 0.1 micron (BP pressure:  $17 \text{ kg/cm}^2$ ) is installed by mistake, the pressure upon lapse of the time  $t_3$  after the resumption of pressure increase is higher than 20 the upper limit ( $4 \text{ kg/cm}^2$ ) of the judging range, with the result that a judgment of abnormality is given, and the alarm goes on to complete the test.

If the filter has a flaw or is improperly installed, the primary-side pressure increases as indicated by curve 25 g in Fig. 4 after the initiation of increase of pressure.

0139202

The pressure fails to reach 2 kg/cm<sup>2</sup> even after the lapse of the predetermined time ( $t_1 = 40$  seconds) after the start of pressure increase. Consequently a judgment of abnormality is given, the alarm goes on, and the gas is discharged 5 from the primary side as stated above, whereby the test is completed.

Although the apparatus and method according to the foregoing embodiment are adapted for off-line testing, it is of course possible to incorporate such an apparatus 10 into a line for in-line testing. More specifically, in-line tests can be carried out automatically in sterilized state with use of the sterilizing filtration system presently employed at plants, by incorporating the pressure sensor alone into the line within a sterilization chamber. In 15 this case, the test results obtained in the entire plant can be concentrically monitored or recorded at one location. Further it is possible to incorporate the pressure sensor into the primary side of a housing for a plurality of filters which are repeatedly used for a long period of time, for 20 example, final filters for bottle washer finishing water or air-vent filters for distilled water tanks, and to use the other components of the apparatus commonly for these filters, whereby periodic tests can be conducted automatically within a short period of time without disassembling the line.

25 Fig. 5 shows a sterilizing filtration apparatus

including a membrane filter for automatic filling equipment for a medicinal liquid. The apparatus has incorporated therein an in-line automatic tester for the membrane filter and comprises the following components which are disposed 5 in a substerilization chamber 20 and a sterilization chamber 21.

A filter housing 22 installed in the substerilization chamber 20 has a cartridge membrane filter 23 fixedly accommodated therein. A remote control air discharge valve 10 25 is connected to the upper end of the filter housing 22 by an air discharge pipe 24. The air discharge valve 25 has an air outlet 26 which is thereby opened or closed. The air discharge pipe 24 is provided with a liquid level sensor 27 comprising an optical fiber 67, and a pressure sensor 28. 15 The membrane filter 23 and the filter housing 22 per se have the same construction as those already known.

A preparation container (primary container) 29 for containing the medicinal liquid to be filtered is disposed in the substerilization chamber 20. The container 29 is 20 connected to the primary side of the filter housing 22 by a primary pipe 31 having a first remote control change-over valve 30. A first compressed air source 32 is provided in the substerilization chamber 20 for forcibly sending the medicinal liquid from the container 29 to the primary side 25 of the housing 22 via the primary pipe 31. A sixth remote

control change-over valve 33 and a first regulating valve 34 are provided between the compressed air source 32 and the preparation container 29.

Further disposed in the chamber 20 are a steam source 35 for steam sterilization, a second compressed air source (gas source) 36 for air blowing and for testing the membrane filter 23 for perfection, and a distilled water source 37 for rinsing and for membrane perfection testing.

5       The steam source 35 is connected, by way of a second remote control change-over valve 38 and a third remote control change-over valve 39, to a portion between the filter housing 22 and the first change-over valve 30 on the primary pipe 31. A pressure gauge 40, a seventh remote control change-over valve 41 and a filter 42 are provided

10      between the steam source 35 and the third change-over valve 39. By way of a fourth remote control change-over valve 43, the second compressed air source 36 is connected to the third change-over valve 39. Provided between the air source 36 and the fourth valve 43 are an eighth remote control

15      change-over valve 44, a pressure increase rate setting valve 45 comprising a needle valve, a second regulating valve 46 and a filter 47. A ninth remote control change-over valve 48 is disposed in parallel with the valve 45, and an air discharge valve 49 is provided between the regulating valve 46 and the filter 47. The distilled water source 37 is

20

25

connected to the fourth change-over valve 43 via a fifth remote control change-over valve 49.

A buffer tank (secondary container) 50 for temporarily containing the filtered medicinal liquid is provided in the sterilization chamber 21. The secondary side of the filter housing 22 is connected to the tank 50 by a secondary pipe 51 extending from the chamber 20 into the chamber 21. Via a tenth remote control change-over valve 52, a medicinal liquid inlet pipe 53 and a fluid discharge pipe 54 are connected in parallel with the pipe 51 within the chamber 21. The forward end of the inlet pipe 53 is opposed to an upper inside wall surface of the tank 50, while the lower end of the discharge pipe 54 is positioned at an upper interior portion of the tank 50 centrally thereof. A temperature sensor 55 is provided on the top of the tank 50, and an air discharge valve 56 is connected to an upper portion of the tank 50 via a filter 57. A medicinal liquid outlet pipe 58 connected to the bottom of the tank 54 has a liquid level sensor 59 which is adapted to detect the liquid level within the tank 50 by the liquid pressure. The outlet pipe 58 is connected to a filling machine (not shown) via an eleventh remote control change-over valve 60 and to a steam discharge pipe 62 and a drain pipe 63 via a twelfth remote control change-over valve 61. The pipes 62 and 63 are disposed in the chamber 20. The

steam discharge pipe 62 has a thirteenth remote control change-over valve 64 and a steam trap 65. The drain pipe 63 has a fourteenth remote control change-over valve 66.

Although not shown, the filling equipment is  
5 provided with a control unit comprising a microcomputer for controlling the overall equipment to automatically sterilize and fill the medicinal liquid, for example, in the following manner.

First for steam sterilization, the valves concerned  
10 are controlled so that steam flows from the steam source 35 into the steam discharge pipe 62 through the third and second change-over valves 39, 38, the primary pipe 31, the membrane filter 23 within the housing 22, the secondary pipe 51, the tenth change-over valve 52, the liquid inlet pipe 15 53 and the fluid discharge pipe 54, the buffer tank 50, the liquid outlet pipe 58 and the twelfth change-over valve 61. At this time, the air discharge valve 25 for the housing 22 and the air discharge valve 56 for the buffer tank 50 are both held closed. During the steam sterilization, the  
20 temperature of steam is monitored by the temperature sensor 55 on the buffer tank 50, such that the opening of the seventh change-over valve 41 for the steam source 35 is controlled to obtain the desired temperature.

Next, air is passed from the second compressed  
25 air source 36 into the drain pipe 63 through the ninth change-

over valve 68, the fourth, third and second change-over valves 43, 39, 38, the primary pipe 31, the membrane filter 23 within the housing 22, the secondary pipe 51, the tenth change-over valve 52, the liquid inlet pipe 53 and the 5 fluid discharge pipe 54, the buffer tank 50, the liquid outlet pipe 58 and the twelfth change-over valve 61, by controlling the valves concerned. The air thus blown in removes the remaining condensed water from the components and cools the membrane filter 23. At this time, the air 10 discharge valve 25 for the filter housing 22 is held closed, but the air discharge valve 56 for the buffer tank 50 is open to a suitable degree. During the air blowing, the temperature of air, i.e. the temperature of the membrane filter 22, is monitored by the temperature sensor 55 on 15 the buffer tank 50, such that the supply of air is discontinued when the temperature drops to the desired level.

To rinse the apparatus, distilled water is then passed from the distilled water source 37 into the drain 20 pipe 63 through the fifth, fourth, third and second control valves 49, 43, 39, 38, the primary pipe 31, the membrane filter 23 within the housing 22, the secondary pipe 51, the tenth change-over valve 52, the liquid inlet pipe 53 and the fluid discharge pipe 54, the buffer tank 50, the liquid 25 outlet pipe 58 and the twelfth change-over pipe 61, by

controlling the valves concerned. The components are rinsed and the membrane filter 23 is wetted with the distilled water. At this time, the air discharge valve 25 for the housing 22 is held closed, but the air discharge valve 56 for the buffer tank 50 is open to a suitable degree.

Air is thereafter caused to flow from the second compressed air source 36 into the drain pipe 63 via the pressure increase rate setting valve 45, the fourth, third and second change-over valves 43, 39, 38, the primary pipe 31, 10 the membrane filter 23 within the housing 22, the secondary pipe 51, the tenth change-over valve 52, the liquid inlet pipe 53 and the fluid discharge pipe 54, the buffer tank 50, the liquid outlet pipe 58 and the twelfth change-over valve 61, by controlling the valves concerned, whereby the membrane 15 filter 23 is tested for perfection.

The test is carried out generally in the same manner as is the case with the test apparatus of Fig. 1.

Before the start of the membrane filter perfection test, the eighth change-over valve 44 for the second 20 compressed air source 36 is closed. Prior to testing, the setting valve 45 is adjusted by the operator to a predetermined pressure increase rate. During testing, the air discharge valve 25 for the housing 22 is held closed, but the air discharge valve 56 for the buffer tank 50 is open 25 to a suitable degree.

In this state, the eighth change-over valve 44 is first opened to start testing, causing the second compressed air source 36 to supply air to the primary side of the housing 22 through the setting valve 45.

5 If the housing 22 or the piping system is sealed improperly or the filter 23 is wetted improperly, an alarm is given, and the test is discontinued as is the case with the apparatus of Fig. 1. Further when the filter is larger than 0.2 micron in pore size, e.g. when a filter having  
10 a pore size of 0.45 micron is installed by mistake, or if the filter is smaller than 0.2 micron in pore size, e.g. if a filter having a pore size of 0.1 micron is installed by mistake, an alarm is given, whereupon the test is discontinued. Further when the filter has a defect or is improp-  
15 erly installed, an alarm is given, whereupon the test is discontinued.

When the membrane filter is completely tested and found to be normal, valves are so controlled as to cause the first compressed air source 32 to send air into the preparation container 29, such that the resulting pressure will cause the medicinal liquid to flow from the container 29 into the filling machine by way of the membrane filter 23 within the housing 22, the secondary pipe 51, the tenth change-over valve 52, the liquid inlet pipe 53, the buffer tank 50, the liquid outlet pipe 58 and the eleventh change-

over valve 60. In this state, air is removed from the filter housing 22 first, and the medicinal liquid is then filtered for sterilization. In the meantime, the air discharge valve 56 for the buffer tank 50 is held open to 5 a suitable degree, while the air discharge valve 25 for the housing 22 is opened before the start of deaeration or venting of the filter housing 22. When the medicinal liquid is supplied to the housing 22 via the primary pipe 31 in this state, the air at the primary side of the housing is 10 forced out from the air outlet 26 via the air discharge pipe 24 and valve 25, permitting the liquid level within the housing 22 to rise gradually. When the liquid level reaches the liquid level sensor 27, this is detected in the following manner, whereupon the air discharge valve 25 is 15 closed to complete the removal of air. With reference to Fig. 6, the forward end of the optical fiber 67 constituting the liquid level sensor 27 is positioned slightly inside the air discharge pipe 24, such that the light transmitted through the optical fiber is partially reflected at the 20 forward end and returned through the fiber. The reflectance of light at the end of the optical fiber 67 differs depending on whether the liquid level is below or at the fiber end, i.e. whether the fiber end is exposed to air or the medicinal liquid. Thus, the amount of returning light 25 varies, and the liquid level reaching the optical fiber 67

is detected by the variation. The liquid level sensor 27 comprising the optical fiber 67 has very high responsiveness, so that the discharge valve 25 can be closed immediately when the liquid level reaches the sensor 27. Air 5 may be removed from the filter housing 22 manually as heretofore done.

When the filter housing 22 has been completely vented with the closing of the air discharge valve 25, the medicinal liquid is sterilized by filtration in the same state. The liquid sent from the preparation container 29 10 to the primary side of the filter housing 22 through the primary pipe 31 is filtered by the membrane filter 23, flows to the secondary side and enters the buffer tank 50 via the secondary pipe 51 and the liquid inlet pipe 53. Four liquid 15 levels are set for the buffer tank 50; i.e. an allowable lower limit, a reference lower limit, a reference upper limit, and an allowable upper limit, as arranged in the ascending order. The eleventh change-over valve 60 is held closed immediately after the start of filtration, and when 20 the liquid level within the tank 50 reaches the reference upper limit, the valve 60 opens, whereby the liquid in the tank 50 is fed to the filling machine via the outlet pipe 58 and the valve 60. The rate of supply of the medicinal liquid to the tank 50 from the inlet pipe 53 is adjusted to 25 a value slightly larger than the rate of discharge of the

liquid from the outlet pipe 58, so that when the liquid level reaches the reference upper limit, the first change-over valve 30 closes to interrupt filtration. When the liquid level within the tank 50 lowers to the reference 5 lower limit, the first change-over valve 30 opens to resume filtration. In this way, the liquid level within the tank 50 is maintained between the reference upper and lower limits during filtration.

When the liquid within the preparation container 10 29 has been wholly sent to the filter housing 22 and filtered, the container 29, the primary pipe 31 and the primary side of the housing 22 are full of air. However, this air, having a pressure lower than the BP pressure, will not pass through the filter 23, permitting the membrane 15 filter to remain wet with the medicinal liquid. The filtrate is entirely sent to the tank 50 under gravity, and the liquid level within the tank 50 gradually lowers. The eleventh change-over valve 60 is closed to finish 20 filtration immediately when the liquid level reaches the allowable lower limit or a predetermined period of time thereafter. When no medicinal liquid remains in the preparation container 29 at this time, this indicates that the filtration has been completed normally. If some medicinal 25 liquid remains in the container 29 when the liquid level within the tank 50 lowers to the allowable lower limit,

the remainder is interpreted as indicating an abnormality occurring somewhere in the apparatus, and an alarm is given. The liquid level reaching the allowable upper limit within the tank 50 is also interpreted as being indicative of an 5 abnormality, and an alarm is given.

After the completion of filtration, the membrane filter 23 is tested again for perfection in order to check whether the filter 23 has functioned normally. Since the membrane filter 23 is wet with the medicinal liquid at this 10 time as stated above, apparatus operates in the same manner as when distilled water is used although values are different.

When the membrane filter perfection test is completed, the filter 23 is manually removed from the housing 22, and the apparatus is cleaned with distilled water 15 in the same manner as when distilled water is used for rinsing previously. At this time, a washing agent, organic solvent or the like may be used in place of distilled water.

Finally, the apparatus is dried in the same manner as the previous air blowing to complete the sterilizing 20 filtration operation.

Although the membrane filter 23 is tested for perfection only before and after filtration, the filter can be so tested with use of the medicinal liquid in the same manner as above at a suitable time during filtration, for 25 example, during interruption following the rise of the liquid

level to the reference upper limit within the tank 50, whereby improved reliability is achieved.

The membrane filter 23 and the housing 22 are not limited to those of the foregoing embodiment in construction but can be modified suitably. Figs. 7 and 8 show different housings 22 for cartridge membrane filters 23, while Fig. 9 shows a disk-like membrane filter and a housing 22 therefor. Throughout the drawings showing filters and housings, like parts are referred to by like reference numerals. Further the membrane filter 23 may be tested for perfection with use of a suitable gas other than air.

The sterilizing filtration apparatus need not always be connected directly to the filling machine unlike the foregoing embodiment. The present invention is of course applicable to liquids other than medicinal liquids. The medicinal liquid sterilizing filtration apparatus described above is merely an embodiment of the invention, and the invention is of course not limited thereto.

## CLAIMS

1. A membrane filter testing method characterized by increasing the pressure at the primary side of a membrane filter fixedly accommodated in a housing and wetted with a liquid, by a gas at a predetermined rate, and checking 5 whether the pressure at the primary side of the membrane filter is within a specified judging range after lapse of a predetermined period of time.

2. A method as defined in claim 1 further characterized by interrupting the increase of pressure for a predetermined period of time upon the primary-side pressure reaching a predetermined level lower than the lower limit of 5 the judging range and checking whether the primary-side pressure decreases during the interruption.

3. A membrane filter testing apparatus characterized in that the apparatus comprises a gas source connectable to the primary side of a membrane filter fixedly accommodated in a housing and wetted with a liquid, pressure increase 5 rate setting means positionable between the gas source and the primary side of the membrane filter to maintain the rate of increase of the pressure at the primary side of the membrane filter by the gas at a predetermined value, a pressure sensor positionable at the primary side of the 10 membrane filter, and a circuit for checking whether the pressure at the primary side of the membrane filter is within

a specified judging range a predetermined period of time after the start of increase of the pressure at the primary side of the membrane filter by the gas.

4. An apparatus as defined in claim 3 wherein the circuit interrupts the increase of pressure for a predetermined period of time upon the primary-side pressure reaching a predetermined level lower than the lower limit of the 5 judging range and checks whether the primary-side pressure decreases during the interruption.

5. An apparatus as defined in claim 3 or 4 wherein the pressure increase rate setting means comprises a needle valve.

6. A liquid sterilizing filtration apparatus comprising a filter housing for fixedly accommodating a membrane filter therein, a primary container for containing a prefilt, a primary pipe connecting the primary side of 5 the filter housing to the primary container, a secondary container for containing a filtrate, and a secondary pipe connecting the secondary side of the filter housing to the secondary container, the apparatus being characterized in that a steam source, a gas source and a distilled water 0 source are connected to the primary pipe via a change-over valve, pressure increase rate setting means being provided between the gas source and the change-over valve for maintaining the rate of increase of the pressure at the primary

side of the membrane filter by a gas at a predetermined  
15 value, a gas outlet being provided at an upper portion of  
the filter housing and openable by a valve, a pressure  
sensor being provided at the primary side of the filter  
housing.

7. An apparatus as defined in claim 6 wherein the  
pressure increase rate setting means comprises a needle  
valve.

8. A liquid sterilizing filtration apparatus  
comprising a filter housing for fixedly accommodating a  
membrane filter therein, a primary container for containing  
a prefilt, a primary pipe connecting the primary side of  
5 the filter housing to the primary container, a secondary  
container for containing a filtrate, and a secondary pipe  
connecting the secondary side of the filter housing to the  
secondary container, the apparatus being characterized in  
that a steam source, a gas source and a distilled water  
10 source are connected to the primary pipe via a change-over  
valve, pressure increase rate setting means being provided  
between the gas source and the change-over valve for main-  
taining the rate of increase of the pressure at the primary  
side of the membrane filter by a gas at a predetermined  
15 value, a gas outlet being provided at an upper portion of  
the filter housing and openable by a valve, a liquid level  
sensor being provided on the filter housing and positioned

above the membrane filter, a pressure sensor being provided at the primary side of the filter housing.

9. An apparatus as defined in claim 8 wherein the pressure increase rate setting means comprises a needle valve.

10. An apparatus as defined in claim 8 or 9 wherein the liquid level sensor comprises an optical fiber having a forward end slightly projecting into a portion of the filter housing above the membrane filter, and the light transmitted through the optical fiber is partially reflected at the forward end and returned through the fiber.

11. An apparatus as defined in claim 8 or 9 wherein a gas discharge pipe and a gas discharge valve positioned thereabove are mounted on the upper side of the filter housing, and the gas discharge valve has the gas outlet thereby openable, the gas discharge pipe being provided with the liquid level sensor and the pressure sensor.

12. An apparatus as defined in claim 11 wherein the liquid level sensor comprises an optical fiber having a forward end slightly positioned inside the gas discharge pipe, and the light transmitted through the optical fiber is partially reflected at the forward end and returned through the fiber.

0139202

FIG.1

1/4

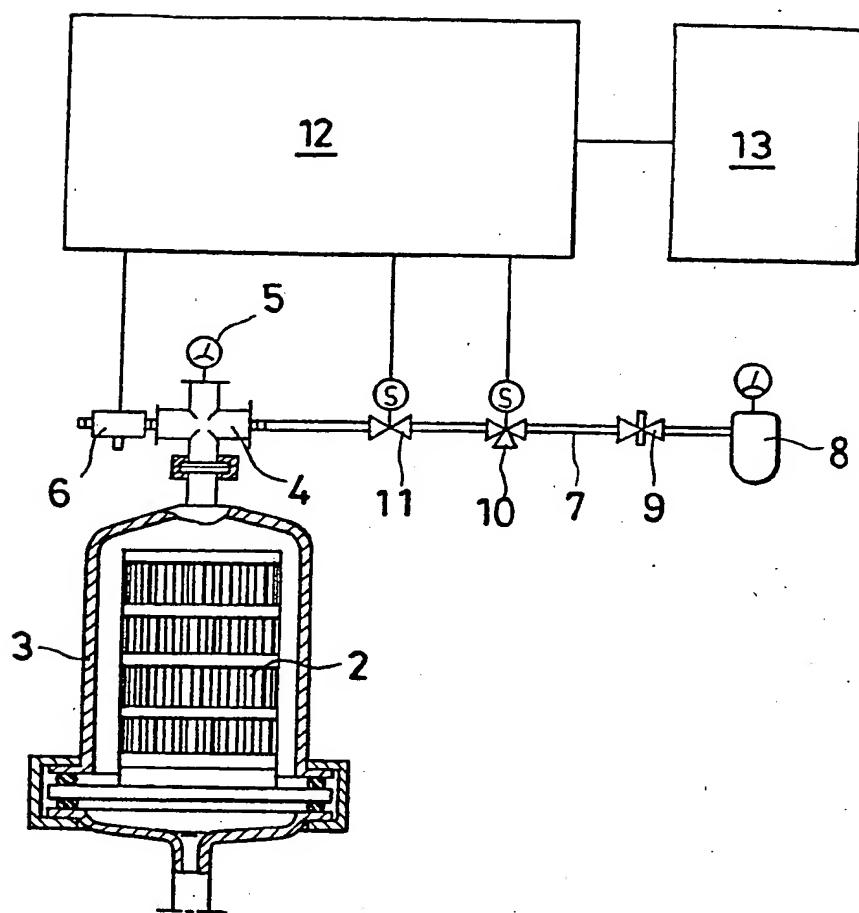
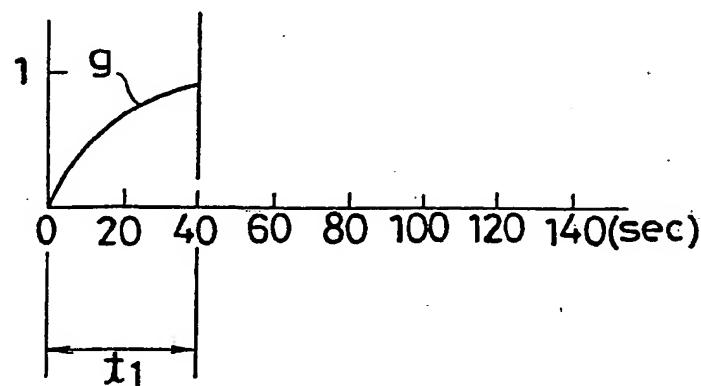
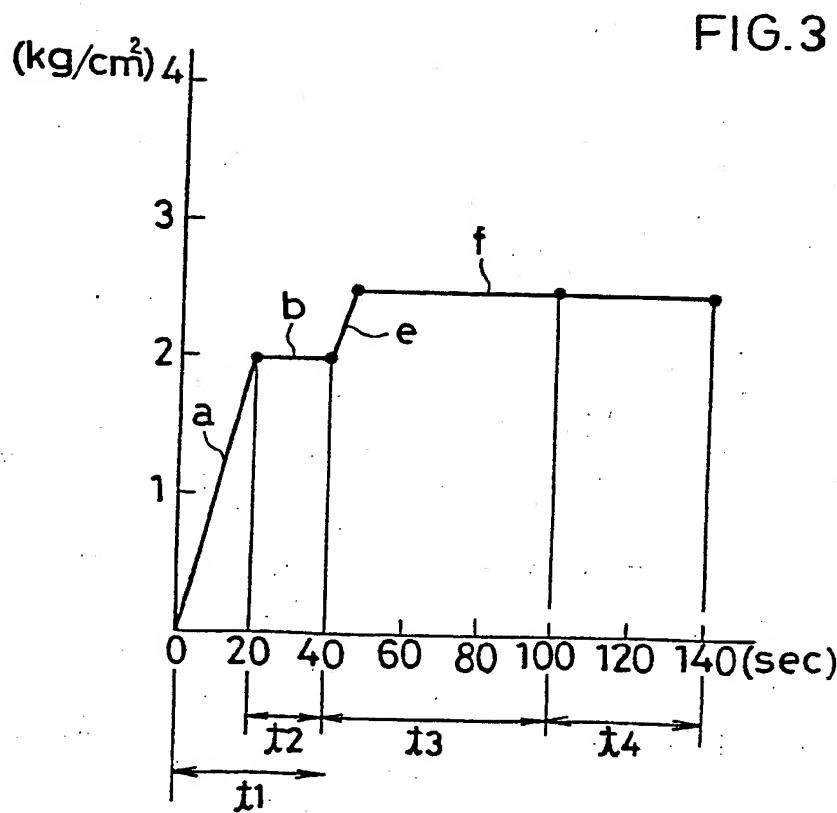
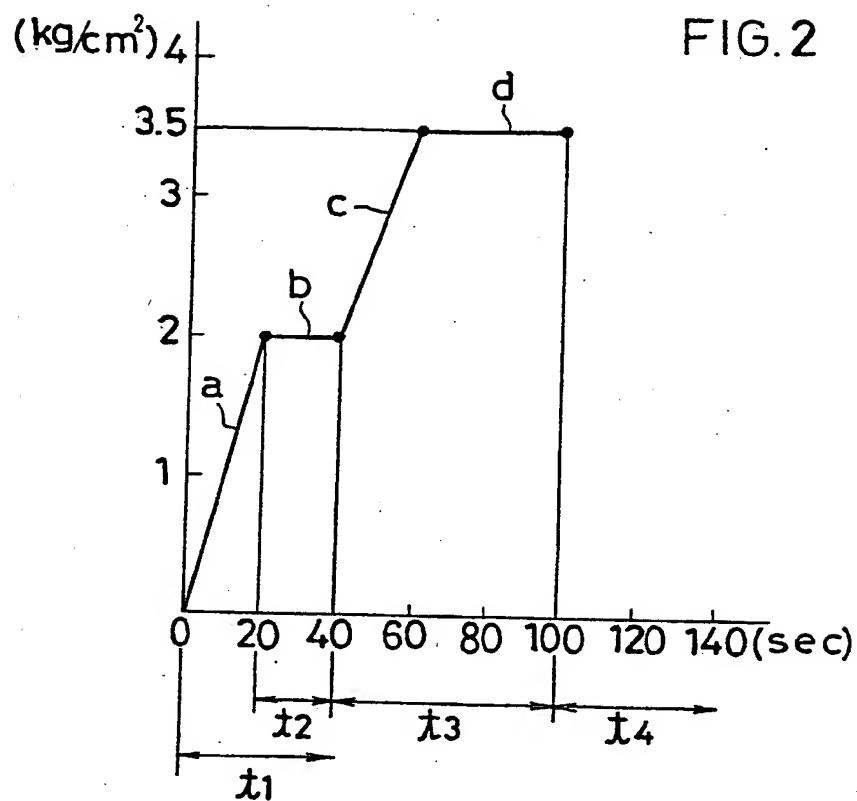


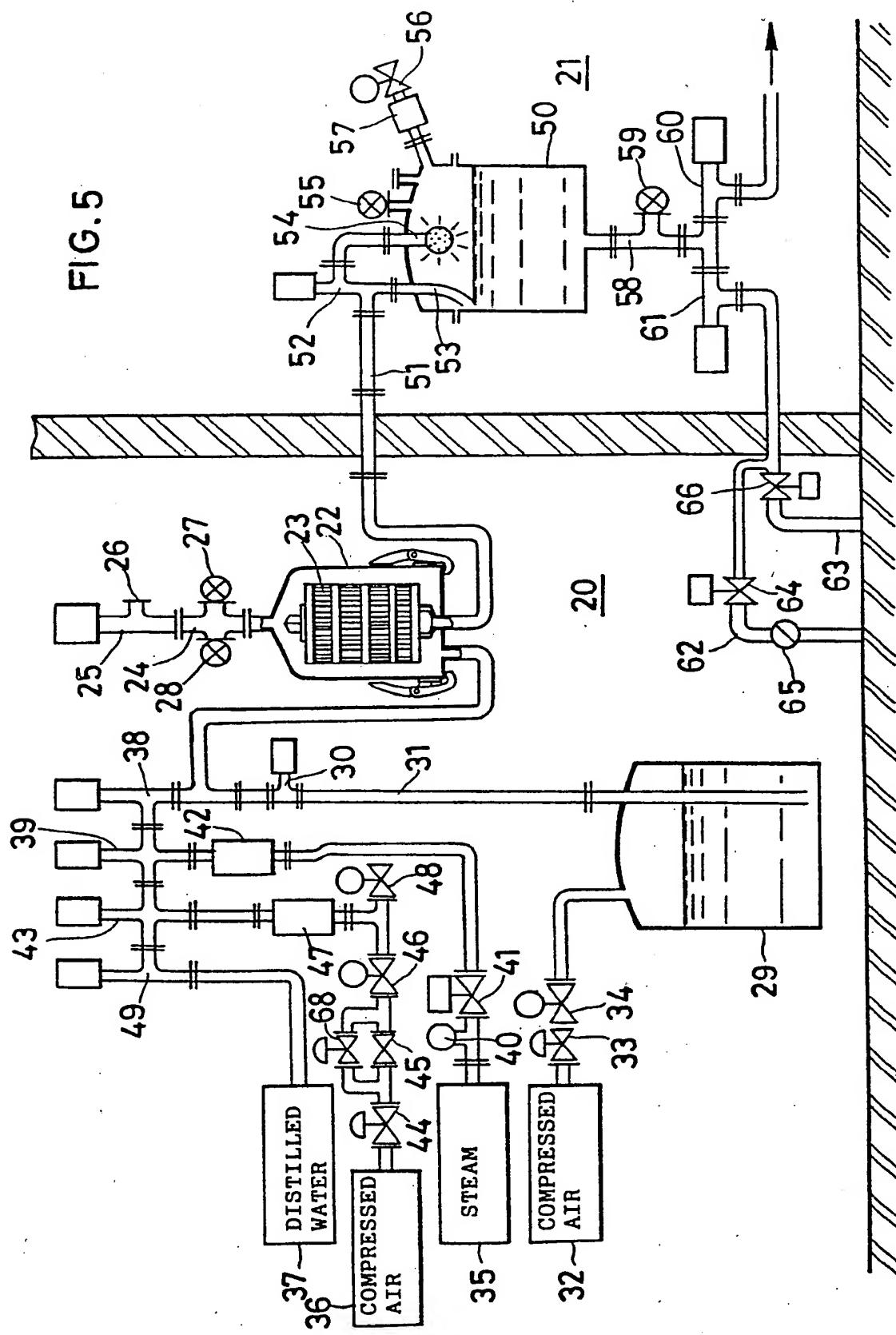
FIG.4



0139202  
1

2 /  
0139202

५



0139202

4/4

FIG.6

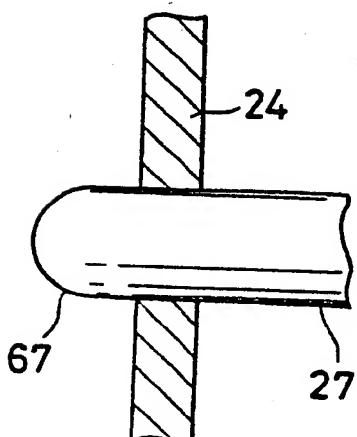


FIG.7

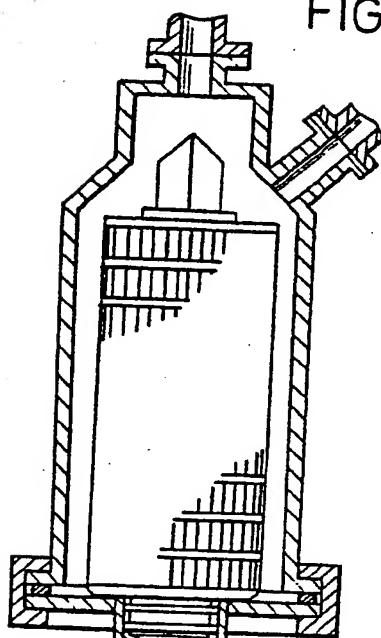


FIG.8

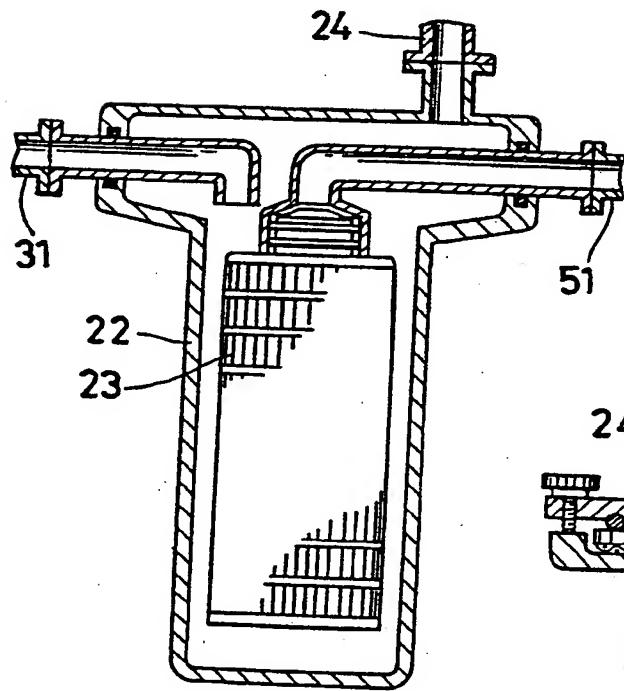
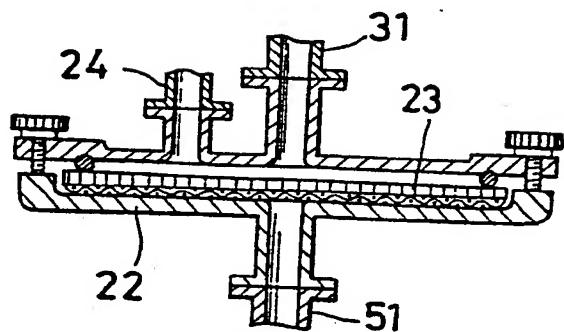


FIG.9





European Patent  
Office

EUROPEAN SEARCH REPORT

0139202  
Application number

EP 84 11 0712

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	EP-A-0 064 159 (B. HUSCHKE) * abstract; figures 1,2; claims 1,2; page 5, line 21 - page 6, line 33; page 1, lines 9-19 *	1-4	G 01 N 15/08 G 01 M 3/26 B 01 D 13/00 A 61 L 2/02 G 01 F 23/28
Y		6,8	
A		5,7,9	
Y	---		
Y	EP-A-0 051 373 (AMF INC.)  * figures 1-3; claims 1, 17-19; page 10, line 22 - page 14, line 23; page 1, lines 18-20 *	6,8,10-12	
A	---	1,3	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	CHEMICAL ENGINEERING PROGRESS, vol. 67, no. 5, May 1971, pages 82-88, New York, US; R.H. HAUSLEIN: "Ultra fine filtration of bulk fluids" * figures 3-5; page 84, column 2, line 1 - page 86, column 2, line 11 *	1,3,6,8	G 01 N B 01 D G 01 M A 61 L G 01 F
Y	DE-A-2 920 199 (EATON S.a.M.)  * figures 1,2,5; claims 1,8,9; page 8, line 30 - page 9, line 1 *	8,10-12	
	---	-/-	
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 28-01-1985	Examiner HOORNAERT P.G.R.J.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



EUROPEAN SEARCH REPORT

0139202  
Application number

EP 84 11 0712

Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	MANUFACTURING CHEMIST AND AEROSOL NEWS, vol. 52, no. 2, February 1981, pages 41-45, London, GB; D. SPRINGETT: "The integrity testing of sterilising membrane filters" * page 41, column 3, line 50 - page 45, column 3, last line; figures 5a-9 *  ----- A FR-A-1 421 388 (COMM. A. L'ENERGIE ATOMIQUE) * figure 1; abstract, point a; page 1, column 1, lines 1-29; page 2, column 1, lines 1-50 *  -----	1,3,6, 8	
		1,3	
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 28-01-1985	Examiner HOORNAERT P.G.R.J.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone			
Y : particularly relevant if combined with another document of the same category			
A : technological background			
O : non-written disclosure			
P : intermediate document			

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

**BLACK BORDERS**

**IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

**FADED TEXT OR DRAWING**

**BLURRED OR ILLEGIBLE TEXT OR DRAWING**

**SKEWED/SLANTED IMAGES**

**COLOR OR BLACK AND WHITE PHOTOGRAPHS**

**GRAY SCALE DOCUMENTS**

**LINES OR MARKS ON ORIGINAL DOCUMENT**

**REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

**OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**